

Efficacy of cilostazol in promoting the maturation of newly created arteriovenous fistula in patients with end-stage renal disease: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND Arteriovenous fistula (AVF) is considered the gold standard for vascular access in hemodialysis. However, achieving the successful maturation of AVF remains a challenge. Cilostazol, a phosphodiesterase-3 inhibitor, has shown promise in enhancing AVF maturation. This study aimed to assess the clinical efficacy of cilostazol in promoting AVF maturation.

METHODS This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive systematic literature search was performed using PubMed, ScienceDirect, Cochrane Library, ProQuest, and Google Scholar to identify studies investigating the efficacy of cilostazol on the maturation of newly created AVF in patients with end-stage renal disease and published up to August 2023. The intervention group received perioperative cilostazol therapy, while the control group did not receive cilostazol. The outcomes were the maturation rate of AVF and AVF-related complications. Meta-analysis was conducted using Review Manager software version 5.3.

RESULTS 5 studies involving 549 patients were included. The intervention group comprised 228 patients, while the control group comprised 321 patients. In the pooled analysis, patients in the intervention group had a significantly higher rate of AVF maturation (odds ratio [OR] = 2.18, 95% confidence interval [CI]: 1.29–3.68, $p = 0.003$, $I^2 = 47\%$) and a lower rate of AVF-related complications (OR = 0.46, 95% CI: 0.28–0.77, $p = 0.003$, $I^2 = 27\%$) compared to the control.

CONCLUSIONS Cilostazol was associated with a higher rate of AVF maturation and a lower rate of AVF-related complications.

KEYWORDS arteriovenous fistula, cilostazol, end-stage renal disease, hemodialysis

Chronic kidney disease (CKD) is a major global public health concern, causing significant morbidity and mortality and affecting approximately 13.4% of the world's population.¹ CKD leads to irreversible renal damage that can further progress to end-stage renal disease (ESRD), which requires renal replacement therapy via either hemodialysis or renal transplantation.² An adequate vascular access is important for the survival of individuals with ESRD who require hemodialysis. Autologous (native)

arteriovenous fistula (AVF) is the ideal hemodialysis access due to its superior patency, fewer complications, and lower costs compared to arteriovenous graft or central venous catheter.³ AVF creation is typically indicated for patients with stage 4 or 5 CKD who will either undergo regular hemodialysis or have initiated hemodialysis using temporary vascular access.⁴

One significant factor contributing to the mortality of patients undergoing hemodialysis is vascular access malfunction, which remains a complex clinical

challenge.⁵ The maturation of the AVF can occur 4–6 weeks after surgery.⁶ In some patients, the fistula may not be usable for hemodialysis until 3 months after surgery due to maturation failure, known as primary maturation failure.⁶ The reported incidence of primary maturation failure ranges from 20% to 60%.^{7,8} The delayed usability of AVF due to maturation failure can result in prolonged dependence on temporary vascular access, increasing the risk of complications and decreasing quality of life. Therefore, efforts to optimize AVF maturation are vital for improving patient outcomes, reducing healthcare costs, and improving the long-term survival of patients. Implementing effective strategies to enhance AVF maturation can significantly alleviate the strain on healthcare resources and improve patients' overall well-being.⁹

Stenosis and thrombosis are the frequent causes of AVF maturation failure.¹⁰ Antiplatelet drugs are among the most discussed medications used to lower the rate of vascular access thrombosis. However, limited and often conflicting data regarding the effectiveness of antiplatelet medications are available.^{11–13} Intimal hyperplasia (or neointima formation), a key histopathological factor, forms the basis of AVF maturation failure. Venous stenosis in fistulas or graft failures is often characterized by intimal hyperplasia. Medications that regulate this pathway may improve AVF maturation.^{14,15}

Cilostazol, a phosphodiesterase-3 (PDE-3) inhibitor with antiplatelet properties, exhibits vasodilatory effects and inhibits smooth muscle proliferation. Theoretically, these mechanisms may inhibit intimal hyperplasia and contribute to AVF maturation.¹⁶ Therefore, this review and meta-analysis aimed to investigate the clinical efficacy of cilostazol in promoting AVF maturation among patients with ESRD and to provide valuable insights regarding the potential benefits of cilostazol as an adjunct therapy for AVF maturation.

METHODS

Study registration

This study protocol was registered in PROSPERO with the registration number CRD42023447040.

Search strategy

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews

and Meta-Analyses guidelines.¹⁷ A comprehensive systematic literature search of electronic databases, including PubMed, Cochrane Library, ScienceDirect, ProQuest, and Google Scholar, was conducted to identify relevant studies published between January 2010 and August 2023. A combination of the following keywords was used: “cilostazol” AND “maturation” AND (“arteriovenous fistula” OR “AV fistula”) AND (“hemodialysis” OR “chronic kidney disease” OR “end-stage renal disease”). There were no limitations regarding country of origin or publication language. Furthermore, the references cited in the relevant papers were manually searched to identify additional relevant articles.

Inclusion and exclusion criteria

Original research including cross-sectional, case-control, cohort, or randomized controlled trial (RCT) studies that included patients with ESRD undergoing AVF creation for the first time and compared AVF maturation between a group of patients receiving perioperative cilostazol therapy and a control group not receiving cilostazol therapy were included in this meta-analysis. Included studies had adequate data available to calculate the odds ratios (ORs) for dichotomous variables or weighted mean differences (WMD) for continuous variables, along with the corresponding 95% confidence interval (CI), and were available as full-text studies. Case reports, review articles, editorials, letters, conference abstracts, animal studies, and duplicate or overlapping studies were excluded from this meta-analysis.

Definition of outcomes

The primary outcome was the AVF maturation rate, and the secondary outcome was the AVF-related complication rate. AVF maturation was defined as the successful use of the AVF for hemodialysis. AVF complications were defined as any serious vascular access event, including thrombosis, vascular access-related infection, reoperation, the requirement of interventions to maintain patency, and steal syndrome.

Data extraction and quality assessment

Three authors (HAW, ES, and R) independently performed the data extraction and evaluated the quality of the included studies. In cases of disagreement, the fourth and fifth authors (AAS

and HK) participated in the discussions to reach a resolution. Data collected from the relevant articles included the first author's name, publication year, study location, study design, participant characteristics, sample size, intervention, outcomes, data required for calculating the OR or WMD, and the corresponding 95% CI. The Jadad score was used to assess the quality of RCTs, and the Newcastle-Ottawa scale (NOS) was used to assess the quality of other studies. The total Jadad score ranged from 1–5 points, assessing randomization (0–2 points), blinding (0–2 points), and withdrawals (0–1 points). A study with a total Jadad score of three points or higher was classified as high quality and that with a score of two points or lower as low quality.¹⁸ The total NOS score ranged from 0–9 stars based on three criteria: patient selection (0–4 stars), comparability of study groups (0–2 stars), and outcome assessment (0–3 stars). A total NOS score of 7 stars or higher was used to define high quality, while scores of 5–6 stars indicated moderate quality and scores of 4 stars or lower indicated low quality.¹⁹

Statistical analysis

All statistical analyses were performed using Review Manager software version 5.3 (The Nordic Cochrane Centre, Copenhagen). A meta-analysis was performed using OR for dichotomous variables or WMD for continuous variables, along with the corresponding 95% CI. Heterogeneity among the included studies was assessed using Cochran's Q chi-square test and I^2 statistics. A fixed-effects model was used when no significant heterogeneity ($p \geq 0.05$ and $I^2 \leq 50\%$) was observed. However, a random-effects model was used when significant heterogeneity ($p < 0.05$ or $I^2 > 50\%$) was observed. A p -value < 0.05 was considered statistically significant for all test statistics. Potential publication biases were assessed using funnel plots.

RESULTS

Literature search

Of 133 potential articles in the initial identification, 5 were included in the meta-analysis. The flowchart of the literature search process can be seen in Figure 1.

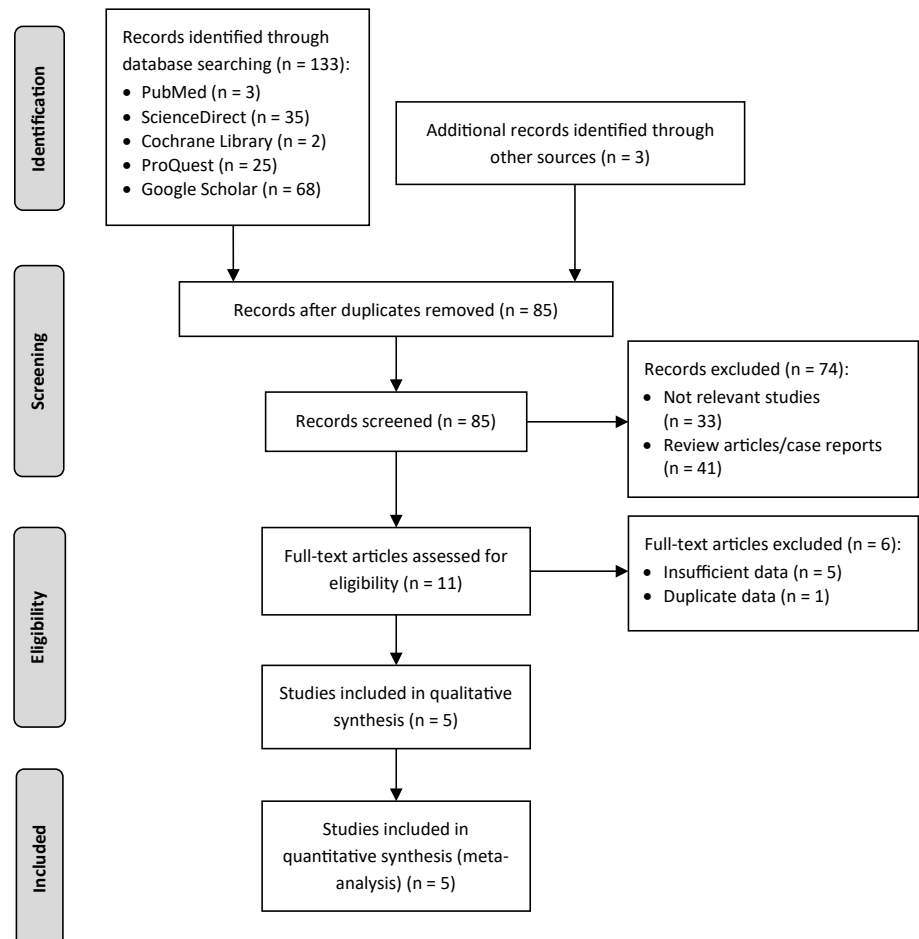


Figure 1. Literature search flow chart

Study characteristics and quality assessment

Five studies involving 549 patients with ESRD who underwent AVF creation surgery were included in the meta-analysis (Table 1).^{20–24} The studies were conducted between 2010 and 2022. One study was an RCT conducted in Iran.²⁰ The mean age of the participants ranged from 42–68 years. The RCT had a total Jadad score of 4, indicating high quality. The NOS scores of the remaining four studies ranged from 7 to 8, indicating high quality.

Effects of cilostazol on AVF maturation

All five included studies reported data regarding AVF maturation.^{20–24} AVF maturation was achieved in 89.5% of patients in the cilostazol group and 75.1% in the control group. No significant heterogeneity was observed among the studies. The pooled analysis using a fixed-effects model revealed a significant association between the use of cilostazol and higher AVF maturation rates compared to the control group (OR = 2.18; 95% CI = 1.29–3.68; $p = 0.003$) (Figure 2).

Effects of cilostazol on AVF-related complications

Two studies reported data regarding AVF-related complications, including thrombosis, infection, reoperation, interventions required to maintain

patency, and steal syndrome.^{21,23} AVF-related complications occurred in 45.7% of patients in the cilostazol group and 74.9% of patients in the control group. No significant heterogeneity was observed among the studies. The pooled analysis using a fixed-effects model revealed a significant association between the use of cilostazol and lower rates of AVF-related complications compared to the control group (OR = 0.46; 95% CI = 0.28–0.77; $p = 0.003$) (Figure 3).

Publication bias

The funnel plot cannot be conducted due to the limited number of the included studies.

DISCUSSION

In this meta-analysis, patients in the cilostazol group were more than twice as likely to experience successful AVF maturation than those in the control group. Furthermore, the patients in the cilostazol group had a lower risk of AVF-related complications. These findings offer new insights regarding the potential of cilostazol, suggesting that it plays a pivotal role in overcoming the challenges associated with AVF maturation.

Table 1. Characteristics of the included studies in the meta-analysis

First author, year	Country	Study design	Sample size (n)	Age (years), mean	Intervention group	Outcome	Quality
Kazemzadeh, ²⁰ 2022	Iran	RCT	60	42	Standard treatment with cilostazol 50 mg 2 times/day immediately after surgery, continued by 100 mg 2 times/day until the maturation of fistula or for a maximum of 12 weeks (n = 30)	Maturation of AVF	4 of 5 points of JS
Jeon, ²¹ 2021	Korea	ROS	194	65	Standard treatment with cilostazol 100 mg 2 times/day before or within 3 days after surgery for a minimum of 2 months (n = 107)	AVF-related complication	8 of 9 stars of NOS
Türkyilmaz, ²² 2018	Turkey	POS	60	54	Standard treatment with cilostazol 100 mg 2 times/day before and after surgery (n = 30)	Maturation of AVF	7 of 9 stars of NOS
Russell, ²³ 2017	United States	ROS	149	68	Standard treatment with cilostazol 50–100 mg 2 times/day for minimum of 1 month before surgery, continued for minimum of 2 months after surgery (n = 33)	Maturation of AVF and AVF-related complication	8 of 9 stars of NOS
Kim, ²⁴ 2010	Korea	ROS	86	54	Standard treatment with cilostazol 50–100 mg 2 times/day for minimum of 1 month before surgery, continued after surgery (n = 28)	Maturation of AVF	7 of 9 stars of NOS

AVF=arteriovenous fistula; JS=Jadad score; NOS=Newcastle-Ottawa scale; POS=prospective observational study; RCT=randomized controlled trial; ROS=retrospective observational study

The standard treatment in the control group was similar within the interventional group. The control group was given placebo in all studies

Figure 2. Forest plot showing the effect of cilostazol on AVF maturation. AVF=arteriovenous fistula; CI=confidence interval

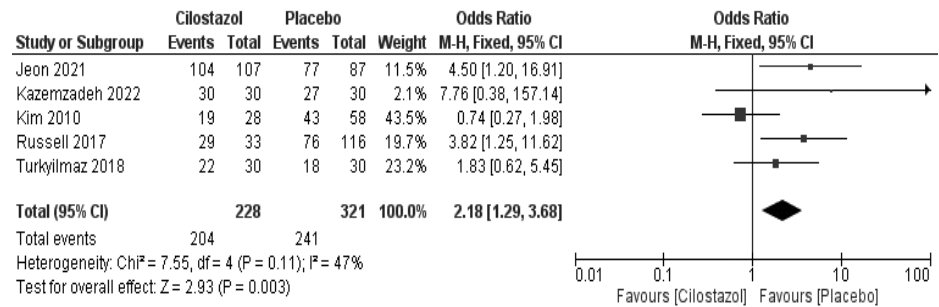
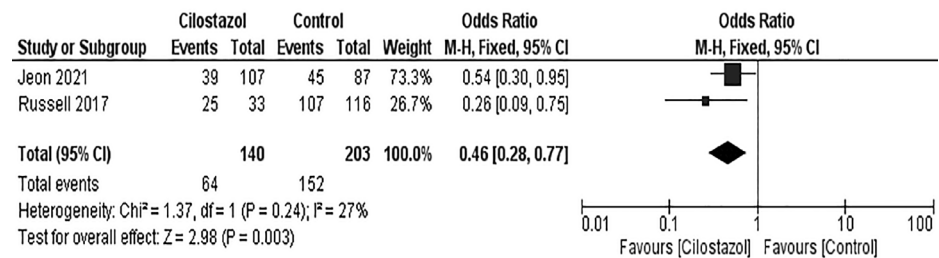


Figure 3. Forest plot showing the effect of cilostazol on AVF-related complication. AVF=arteriovenous fistula; CI=confidence interval



Four of the five studies included in this meta-analysis reported that cilostazol was significantly associated with a more favorable AVF maturation rate.^{20–23} Kim et al²⁴ reported no significant association between the use of cilostazol and AVF maturation, which may have been affected by the small sample size. Two studies reported that cilostazol was significantly associated with reduced AVF-related complications, including thrombosis, vascular access-related infection, reoperation, interventions required to maintain patency, and steal syndrome.^{21,23} Up to 50% of AVFs failed to serve as viable vascular access for hemodialysis, and the rate of reintervention reached 25% within the first 2 years, resulting in physical and cost burdens for patients.^{25,26}

The maturation of the AVF is a critical factor in determining the success of hemodialysis. The ‘rule of six’ defines AVF maturation and includes a minimum blood flow rate of 600 ml/min, location within 6 mm from the skin surface, and a minimum fistula diameter of 6 mm.²⁷ In maturation failure, the new fistula fails to be successfully used for hemodialysis. Risk factors that increase the risk of AVF maturation failure include older age (>65 years), female sex, smoking, hypertension, diabetes, dyslipidemia, obesity, heart failure, severe anemia, and peripheral artery disease (PAD).^{28,29} Patients with these risk factors are considered at high risk of AVF maturation failure, and efforts are required to improve the success of AVF maturation in these patients.³⁰ In the present study, the patients had diverse risk factors, including hypertension, diabetes, smoking, dyslipidemia, cardiovascular diseases,

and PAD. However, these risk factors were equally matched between the intervention and control groups to minimize bias.^{20–24} Although AVF surgical techniques are advancing, the rate of AVF maturation failure remains relatively high, making strategies for improving AVF maturation an ongoing challenge.³¹

Several mechanisms contribute to the pathophysiology of AVF maturation failure. The structural differences between the venous and arterial vascular walls lead to non-physiological pressure in the venous outflow tract. To accommodate this, the venous outflow tract needs to undergo arterialization, which involves thickening of the vessel wall to withstand increased pressure and tensile stress. Additionally, the luminal diameter must expand to promote improved blood flow and adapt to increased shear stress.^{32,33} Due to this complex process, the venous outflow tract or the area near the AVF connection (juxta-anastomotic region) is often responsible for AVF maturation and luminal stenosis, possibly due to thrombosis and the development of intimal hyperplasia in the AVF venous outflow tract.^{34,35} Thrombosis plays a minor role in the failure of fistula maturation, and intimal hyperplasia is a more significant mechanism.^{36,37}

Intimal hyperplasia is an inflammatory process triggered by injury that leads to thickening of the intimal layer, proliferation of vascular smooth muscle cells (VSMCs), and deposition of extracellular matrix. As intimal hyperplasia progresses, it causes stenosis within the AVF, disrupting the hemodynamics and flow and ultimately resulting in thrombosis and AVF failure.^{15,38} This process is initiated by endothelial injury

and is often caused by surgical trauma and alterations in flow dynamics as the vein undergoes arterialization. Unlike atherosclerosis, which develops gradually as a chronic inflammatory disease, intimal hyperplasia is a rapid adaptive response to various stressors, such as surgical procedures, hemodynamic changes, immune responses, and metabolic stress. An understanding of this process is crucial to address AVF maturation complications, and research regarding methods to inhibit this pathway is necessary.^{39,40}

To date, no drugs have gained approval specifically for inhibiting intimal hyperplasia.⁴¹ Cilostazol is a specific PDE-3 inhibitor that increases intracellular cyclic adenosine monophosphate and activates protein kinase A. It exhibits various pharmacological effects, including vasodilation, inhibition of platelet activation and aggregation, anti-inflammatory effects, thrombosis prevention, improved blood flow to the extremities, and inhibition of VSMC proliferation. Due to these beneficial effects, cilostazol is widely used in vascular medicine, especially in treating PAD.^{42,43} Cilostazol might also be theoretically beneficial for AVF maturation, as it was effective in patients with ESRD who experienced a pathophysiological process similar to intimal hyperplasia causing AVF failure.⁴⁴

The properties of cilostazol may influence AVF stenosis by reducing the pathway of intimal hyperplasia through the inhibition of VSMC proliferation.⁴⁵ In a recent experimental study by Karagöz et al,⁴⁶ cilostazol demonstrated an inhibitory effect on intimal hyperplasia and VSMC proliferation after vascular anastomosis in a rabbit model. Based on the current meta-analysis, cilostazol has emerged as a promising candidate for further research and development of AVF maturation. However, its safety profile in patients undergoing AVF surgery remains unclear. RCTs with larger sample sizes are needed to evaluate the efficacy and safety of cilostazol for enhancing AVF maturation. These findings are expected to offer valuable insights regarding the development of AVF guidelines.

This study had several limitations. First, the included studies were sourced only from Iran, Korea, Turkey, and the United States, which may limit their representativeness of the global population. Second, the number of studies was relatively small, with only one RCT and two reports regarding AVF-related complications. Third, guidance regarding the optimal dosage and duration of cilostazol use in patients undergoing AVF surgery is lacking. Fourth, a funnel plot

could not be constructed due to the limitations of the studies; therefore, publication bias cannot be ruled out. Few studies have examined the effects of cilostazol on AVF maturation. Future research should focus on larger, well-designed RCTs to confirm these findings and provide more precise estimates of the efficacy and safety of cilostazol during AVF maturation.

In conclusion, perioperative cilostazol therapy was associated with a higher rate of AVF maturation and a lower rate of AVF-related complications in patients with ESRD. Cilostazol may be valuable in improving outcomes in patients undergoing AVF creation, potentially leading to better access to hemodialysis for patients with ESRD. Further investigations and clinical trials are necessary to refine the efficacy and safety of cilostazol in patients undergoing AVF creation and to establish optimal dosing and timing.

Conflict of Interest

The authors affirm no conflict of interest in this study. An abstract of this paper was previously presented as a poster presentation at the 14th Annual Scientific Meeting of Indonesian Association of Thoracic, Cardiac, and Vascular Surgeons (PIT HBTkVI, October 18–21, 2023, Bali, Indonesia).

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